

REMARKS

Claim 58 has been amended to correct an inadvertent typographical error. No new matter has been added by the amendments.

Claims 18-81 are pending in the application, with claims 18, 34, 39, 58 and 66 being the independent claims. Claims 34 and 38 have been withdrawn from consideration by the Examiner.

Applicants respectfully traverse all of the rejections in the Office Action and note their intention to appeal these rejections should a further Office Action in the merits be issued.

I. The Objection to Claim 58 Should be Withdrawn

Claim 58 has been objected to at page 2 of the Office Action, suggesting that the term “submergin” should read “submerging.” Applicants thank the Examiner for identifying this inadvertent typographical error. Present claim 58 recites “submerging.” Hence, this objection should be withdrawn.

II. The Rejection of Claims 18-19 and 21-27 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 18-19 and 21-27 have been rejected at pages 2-4 of the Office Action as allegedly being unpatentable over Zimmermann, U.S. Patent No. 6,465,226 (hereinafter “Zimmermann”) in view of Huang *et al.*, *Solid State Ionics* 120:205-210 (1999) (hereinafter “Huang”). Applicants respectfully traverse this rejection.

The Office Action suggests that Zimmermann discloses a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising producing liquid droplets from a solution comprising an ionically crosslinkable polymer into a gas stream using a nebulizing nozzle, and transferring the gas stream into a gelling solution.

The Office Action concedes that Zimmermann does not teach using an ultrasonic nebulizer to form the gas stream. The Office Action attempts to cure this deficiency with the disclosure of Huang, asserting that Huang discloses a process for preparation of a homogeneous, ultrafine powder by generating an aerosol with an ultrasonic nebulizer. The Office Action

continues to assert that it would have been obvious to employ the ultrasonic nebulization method of Huang in Zimmermann, as Huang discloses that atomizing a precursor solution by ultrasonic nebulizer produces homogenous, ultrafine powders having a particle size of about 100 nm. The Office Action also indicates that Zimmermann does not explicitly disclose separating the microspheres from the gelling solution. However, the Office Action suggests that it is inherent that the microspheres are separated from the gelling solution in Zimmermann. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

A) The Combination of Zimmermann and Huang Does Not Disclose the Present Claims

As an initial point, Applicants submit that, contrary to the assertions in the Office Action, it would not have been obvious that the gas stream utilized in the apparatus of Zimmermann is in fact a continuous gas stream. A continuous gas stream is not necessarily required in order to form droplets in the apparatus of Zimmermann. Droplet formation from a nozzle tip is a discontinuous process and, thus, at first glance, a discontinuous gas stream should be required to cause the droplets to break off from the nozzle. Thus, a person of ordinary skill in the art would consider the gas stream of Zimmermann to be discontinuous, rather than continuous, as asserted in the Office Action.

Applicants again also respectfully submit that Zimmermann as modified by Huang does not disclose “transferring the gas stream into a gelling solution comprising di-, multi- or polyvalent ions, whereby crosslinked polymer microspheres are formed,” of present claim 18. Rather, Zimmermann discloses that “the alginate solution [is] dropped into a Petri dish” (*see* Zimmermann at column 3, lines 15-16), which provides the precipitation bath. Applicants continue to submit that a person of ordinary skill in the art would understand that “dropping” the droplets from the nozzle of Zimmermann into the gelling solution is not the same as “transferring the gas stream into” the gelling solution of present claim 18, which clearly requires that the gas *stream itself* enters into the gelling solution, rather than simply allow *droplets* to drop from the gas stream onto the surface of the gelling solution, as set forth in Zimmermann.

Applicants respectfully submit that a person of ordinary skill in the art would understand that simply dropping nebulized droplets onto the surface of a gelling solution, as suggested by

Zimmermann, would most likely not actually allow the nebulized droplets to enter the gelling solution, as required by the presently claimed invention. Production of droplets via nebulization results in a “mist” of droplets that, if simply dropped onto the surface of a gelling solution would most likely simply float above the surface of the liquid (as in an air humidifier), or produce a film on top of the gelling solution, thus not allowing for the formation, and ultimate separation, of polymer microspheres. Applicants submit that the combination of Zimmerman and Huang does not disclose all of the required elements of the presently claimed invention. Thus, Applicants submit that the Office Action as not set forth a *prima facie* case of obviousness. See M.P.E.P. § 2143.03.

In response to these arguments, the Office Action asserts that claim 18 does not specify “how the gas stream is ‘transferred’ into the gelling solution.” Office Action at paragraph bridging pages 29-30. The Office Action further asserts, without any evidentiary support, that “it would have been obvious to one of ordinary skill in the art at the time of the invention that transferring the gas stream into a gelling solution would also include dropping droplets onto the surface of a gelling solution.” *Id.*

Applicants respectfully disagree with this contention and submit that one of ordinary skill in the art would clearly understand that transferring a gas stream into a gelling solution, as in present claim 18 and as set forth in the present specification, would specifically *exclude* dropping droplets *on the surface* of the gelling solution.

It is preferred to dip the tubing connecting nebulizing chamber (2) and vessel (9) *as deep as possible into the bath* of the gelling solution (10) to allow the aerosol droplets (13) comprising crosslinkable polymer to interact with the di-, multi- or polyvalent counterions of the gelling solution to form crosslinked microspheres.

Present specification at page 5, third paragraph (emphasis added). Thus, the combination of references cited in the Office Action does not disclose the presently claimed invention.

B) There Is No Reasonable Expectation of Success in Combing Zimmermann and Huang

Applicants also respectfully submit that there is no reasonable expectation of success that the atomic nebulizer disclosed in Huang could be utilized in the methods of Zimmermann to produce droplets of biologically active substance having the size required in Zimmermann. Zimmermann requires that the formed droplets have a diameter that is 1.5 to 4 times the volume

of biologically active substance (islets of Langerhans) that form the cores of the microcapsules. *See* Abstract. This requirement is met by providing the appropriate conditions of air flow and flow rate. *Id.* Applicants submit that there is no indication that the ultrasonic nebulizer disclosed in Huang could produce droplets having the required size characteristics, or even produce droplets of the islets of Langerhans at all.

The ultrasonic nebulizer disclosed in Huang is designed to generate an aerosol of an alcoholic precursor solution that is carried to an ignition nozzle of a flame spray pyrolysis setup, where the aerosol is ignited so as to form an ultrafine powder on the wall of the collector. *See* Huang at page 206, Experimental aspects. In Huang, a precursor solution comprising SnCl_4 or SnCl_2 dissolved in ethanol is aerosolized. Applicants submit that there is not a reasonable expectation of success that simply because the ultrasonic nebulizer in Huang is able to generate an aerosol of these particular materials that it in any way could generate droplets of islets of Langerhans having the requisite diameter of 1.5 to 4 times the volume of the core of biologically active material. As set forth in M.P.E.P. § 2143(D), a *prima facie* case of obviousness can only be shown where the cited combination of references would yield predictable results. *See KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007). The Office Action has not provided a showing that modifying the disclosure of Zimmermann with that of Huang would have a reasonable expectation of success -- i.e., a reasonable expectation of producing the droplets required in the methods of Zimmermann. Absent such a showing, a *prima facie* case of obviousness cannot be established. *See* M.P.E.P. § 2143.02.

In response to these arguments, the Office Action states “[i]t would have been obvious to one of ordinary skill in the art at the time of the invention that the combination of Zimmermann and Huang is likely to produce droplets of biologically active substance of the required size since Zimmermann teaches that the core volume is specified by the starting material.” Office Action at page 30, last paragraph.

Applicants agree that Zimmermann indicates that “the core volume is specified by the starting material and the process used to obtain it.” Zimmermann at column 2, lines 29-30. However, the Office Action still has failed to provide any evidence that the method of Huang would in any way be able to provide the requisite “droplets whose volume comprises more or less 1.5 to 4 times the core volume.” *See* Zimmermann at column 2, line 28. Applicants submit

that there cannot be a reasonable expectation of success of achieving droplets of such a size, based simply on the disclosure of Huang, as Huang is directed to the generation of *aerosols of an alcoholic precursor solution of SnCl₄ of SnCl₂, not a solution of biologically active substances* that comprise the core particles, as in Zimmermann. Applicants submit that the conclusions presented in the Office Action have no evidentiary basis, and thus, clearly cannot support a *prima facie* case of obviousness.

C) Huang Would Render Zimmermann Unsatisfactory for Its Intended Purpose

In addition, Applicants submit that Zimmermann cannot be modified with the disclosure of Huang, as required in Office Action, as such a modification would render Zimmermann unsatisfactory for its intended purpose. As set forth in M.P.E.P. § 2143.01, “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants submit that Zimmermann is directed to the production of microcapsules containing the biologically active material, islets of Langerhans. As noted in Zimmermann, these cells produce insulin, and it is a goal of Zimmermann to “introduce living cells into the human body,” so as to treat diabetes mellitus. *See* Zimmermann at column 1. To encapsulate these cells, it is first necessary to generate droplets of the cells. While Zimmermann utilizes a spray nozzle which focuses airflow to generate the droplets (*see* Zimmermann at column 3, lines 1-5), the Office Action suggests that a person of ordinary skill in the art would have found it obvious to instead utilize the ultrasonic nebulizer of Huang to form the droplets.

Applicants respectfully disagree with this suggestion and note that a person of ordinary skill in the art would not have considered it obvious to utilize the ultrasonic methods of Huang to generate the droplets required in Zimmerman. At the time of filing the present application it was well known that, due to the fragility of islets of Langerhans, application of ultrasound actually *disrupts* the islets, and specifically, the β -cell structure. *See, e.g.,* Parry *et al.*, “Proinsulin Biosynthesis in Broken-Cell Preparations of Islets of Langerhans,” *Biochem J.* 170:523-527 (1978). As discussed in Parry, subjecting islets of Langerhans to ultrasound of 1 MHz for 2 seconds (*see* Parry at page 524, first paragraph), destroys the islets and their enzymic machinery.

“It may be concluded that when β -cells are disrupted by ultrasonic methods the enzymic machinery for converting proinsulin to insulin is disorganized . . . [m]icroscopic examination of the cells, moreover, did not suggest the presence of any intact cells in the preparation.” *Id.* at page 526, first column.

Thus, a person of ordinary skill in the art clearly would not have considered it obvious to utilize the ultrasonic nebulizer of Huang, which operates at a similar frequency of 1.63 MHz (*see* Huang at page 206, Experimental aspects) in the methods of Zimmermann, as ultrasound in this range, as demonstrated by Parry, destroys islets of Langerhans and their enzymic machinery. In fact, due to an increased dwell time in the ultrasonic nebulizer that would clearly be longer than the 2 seconds utilized in Parry, a person of ordinary skill in the art would clearly expect such a treatment to destroy, or at least inactivate, the islets. As Zimmermann is directed to methods of encapsulating active cells (i.e., intact, enzymically active), such a modification would clearly render Zimmermann unsatisfactory for its intended purpose. As set forth in M.P.E.P. § 2143.01, such a modification is not allowed, and thus, the Office Action has not set forth a proper *prima facie* case of obviousness.

In response to these arguments, the Office Action asserts, “[i]t would have been obvious to one of ordinary skill in the art at the time of the invention that exposing the core material such as a dead cell or other active substances which are not islets of Langerhans to ultrasound would not render Zimmermann unsatisfactory for its intended purpose.” Office Action at page 31, first paragraph.

Applicants respectfully disagree with these contentions and submit that a person of ordinary skill in the art, reading Zimmermann, would determine that the sole example of the method and apparatus described in Zimmermann is focused on encapsulating active islands of Langerhans. Thus, a person of ordinary skill in the art would not have considered it obvious to modify this disclosure with the ultrasonic nebulizer of Huang, as use of such ultrasound would clearly destroy these cells. Thus, Applicants continue to submit that such a modification would render Zimmermann unsatisfactory for its intended purpose, and as set forth in M.P.E.P. § 2143.01, is not allowed.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

III. The Rejection of Claims 20 and 28 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 20 and 28 have been rejected at pages 4-5 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Lim, U.S. Patent No. 4,352,883 (hereinafter “Lim”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Huang disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the polyvalent cation of the gelling solution is selected from the compositions set forth in present claim 20, or that the metal cation is Ca²⁺, as set forth in present claim 28. The Office Action attempts to cure these deficiencies with the disclosure of Lim, suggesting that Lim discloses the polyvalent cation polyethyleneimine of a gelling solution and the use of Ca²⁺ as the metal cation of a gelling solution. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Lim fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang and Lim, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

IV. The Rejection of Claims 29-30, 32 and 35-37 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 29-30, 32 and 35-37 have been rejected at pages 5-7 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Andersson *et al.*, Published International Patent Application No. WO 03/091315 (hereinafter “Andersson”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Huang disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the gelling solution additionally comprises surfactant present in an amount of from 0.05% to .15% by weight; that the solution of the ionically crosslinkable polyionic polymer is kept within a temperature range of 25 to 35°C; or filtering the microspheres through a screen. The Office Action attempts to cure these deficiencies with the disclosure of Andersson, indicating that Andersson discloses the addition of surfactant to a gelling solution, and the use of a temperature of 40°C, and filtering beads through a sieve. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Andersson fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang and Andersson, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

V. The Rejection of Claim 31 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 31 has been rejected at page 7 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and Andersson and further in view of Lemoine *et al.*, *International Journal of Pharmaceutics* 176:9-19 (1998) (hereinafter “Lemoine”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the surfactant is selected from those compositions set forth in present claim 31. The Office Action attempts to cure these deficiencies with the disclosure of Lemoine, indicating that Lemoine discloses the use of polyoxyethylene sorbitan trioleate as a surfactant in the production of alginate microspheres.

The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Andersson and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VI. The Rejection of Claim 33 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 33 has been rejected at pages 8-10 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Vasington *et al.*, U.S. Patent No. 5,387,522 (hereinafter “Vasington”), Anderson and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Andersson and Lemoine disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises 0.75% to 1.5% by weight of sodium alginate. The Office Action attempts to cure these deficiencies with the disclosure of Vasington, indicating that Vasington discloses the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness. Vasington, Andersson and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann. Thus, Zimmermann, Huang, Vasington, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VII. The Rejection of Claims 39-49 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 39-49 have been rejected at pages 10-12 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and further in view of Lim. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Huang disclose the claimed invention as set forth above. The Office Action concedes, however, that the combination of Zimmermann and Huang does not disclose “submerging the gas stream via a tubing comprising dispenser holes.” The Office Action attempts to cure this deficiency with the disclosure of Lim, suggesting that Lim discloses a process for encapsulation of biological material by forcing a tissue suspension through a vibrating capillary tube that is immersed in a solution of sodium alginate. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to submerge the gas stream of Zimmermann via a tubing into a gelling solution. Applicants respectfully disagree with these contentions and conclusions.

As an initial matter, as set forth above, Applicants submit that the combination of Zimmermann and Huang does not support a *prima facie* case of obviousness regarding the other elements of claim 39. However, even if Zimmermann and Huang could be properly combined, a person of ordinary skill in the art would not have considered it obvious to modify this combination of references with the disclosure of Lim so as to arrive at the presently claimed invention.

As an initial matter, Applicants note that Lim does not disclose “submerging a gas stream” into a gelling solution, as asserted by the Office Action. Rather, Lim specifically indicates that the capillary carrying the tissue suspension is “positioned *within hollow region* 16 of the vortex.” Lim at column 6, lines 16-17 (emphasis added). Thus, Lim specifically points out that the tip of the capillary is *not submerged* into the gelling solution, and thus, a gas stream and droplets emerging from this tip could not be “submerged” as required in the presently claimed invention.

The Office Action suggests that Huang could be utilized to generate liquid aerosol droplets from a solution that are then passed out of the nozzle apparatus disclosed in

Zimmermann. The Office Action further asserts that the output from the nozzle apparatus of Zimmermann could then be connected to the capillary of Lim, and directed to a gelling solution. See Office Action at pages 3 and 10. Applicants submit that not only is there no reasonable expectation of success of assembling a process in this manner, but it in fact would not even be technically feasible to a person of ordinary skill in the art.

Applicants note that Lim utilizes a vibrating capillary to generate appropriately sized droplets of a tissue suspension. See Lim at column 6, lines 20-30; column 9, lines 24-27 (“[d]roplets on the order of 300-400 microns in diameter are thrown from the tip of the capillary”) However, following the reasoning suggested by the Office Action, appropriately sized droplets of tissue suspension *would have already been generated* using the nebulizing apparatus of Huang in the combination of Zimmermann and Huang. Thus, there is no reason for a person of ordinary skill in the art to attempt to *further generate droplets* of a tissue suspension. In fact, it is entirely possible that the nebulized droplets produced from a combination of Huang and Zimmermann (i.e. an atomized solution as noted on page 3 of the Office Action) would not even be able to pass through the capillary tube of Lim. Specifically, Lim describes the capillary utilized in the disclosed process as “a glass capillary having a gradually decreasing diameter ending in a tip of inside diameter of about 300 microns.” Lim at column 9, lines 16-20. The Office Action has provided no showing that a nebulized solution of a tissue suspension (i.e., an aerosol) could in any way be passed through such a capillary tube. Thus, Applicants submit that there can be no reasonable expectation of success of carrying out the method as suggested in the Office Action.

Applicants submit that the Examiner is merely relying on *ex post* reasoning to generate the presently claimed invention. A person of ordinary skill in the art, practicing the process suggested by the Office Action as resulting from the combination of Zimmermann and Huang, would not have looked to *further modify* such a process with yet *another method* for generating droplets, when droplets would have already been generated. In addition, the Examiner has provided no showing as to how the combined disclosures of Zimmermann and Huang could be further modified with a glass capillary tube as disclosed in Lim. Lim discloses that a solution from a beaker is forced through the glass capillary via an infusion pump. See Lim at column 9, lines 14-26. In contrast, the “output” from the device of Zimmermann is generated by a spray

nozzle head. *See* Zimmermann at column 3, lines 1-5. The Office Action has provided no evidence that the glass capillary of Lim could in any way be attached to the nozzle head of Zimmermann.

Applicants submit that a person of ordinary skill in the art would not have considered it obvious to combine all three of these completely disparate references in the way required in the Office Action so as to generate the presently claimed invention. The only rationale for doing so would be impermissible hindsight, based on the disclosure of the present specification. As held in *KSR Intern. Co. v. Teleflex Inc.*, such reasoning cannot support a *prima facie* case of obviousness. 127 S.Ct. 1727, 1742 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant on *ex post* reasoning.”).

In view of the foregoing remarks, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. § 103, should be withdrawn.

VIII. The Rejection of Claims 50-51, 53 and 55-57 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 50-51, 53 and 55-57 have been rejected at pages 12-14 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and Lim and further in view of Andersson. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang and Lim disclose the claimed invention of claim 39 as set forth above. The Office Action, however, indicates that these references do not disclose that the gelling solution comprises a surfactant present at the recited concentration, or that the solutions of the crosslinkable polymer is kept within the recited temperature range. The Office Action attempts to cure these deficiencies with the disclosure of Andersson, suggesting that Andersson discloses the use of a liquid having a reduced surface tension by adding a surfactant, and that the temperature of the polysaccharide solution is kept below about 40°C. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang and Lim does not support a *prima facie* case of obviousness. Andersson fails to cure these

deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim and Andersson, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

IX. The Rejection of Claim 52 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 52 has been rejected at page 14 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang, Lim, Andersson and further in view of Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose a surfactant selected from the recited group. The Office Action attempts to cure these deficiencies with the disclosure of Lemoine, suggesting that Lemoine discloses the use of a polyoxyethylene sorbitan trioleate as a surfactant in the production of alginate microspheres. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang, Lim and Andersson does not support a *prima facie* case of obviousness. Lemoine fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

X. The Rejection of Claim 54 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 54 has been rejected at pages 14-16 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang and Lim and further in view of Vasington, Anderson and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim Andersson and Lemoine disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises 0.75% to 1.5% by weight of sodium alginate or that the sodium alginate is low viscosity. The Office Action attempts to cure these deficiencies with the disclosure of Vasington, indicating that Vasington discloses the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang and Lim does not support a *prima facie* case of obviousness. Vasington, Andersson and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim, Vasington, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

XI. The Rejection of Claims 58-65 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 58-65 have been rejected at pages 17-21 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang, Lim, Andersson and further in view of Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim, Andersson and Lemoine disclose the claimed invention as set forth above, including the

specifically recited amounts of the components. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang, Lim, Andersson and Lemoine does not support a *prima facie* case of obviousness. Applicants submit that none of the cited references demonstrate that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

XII. The Rejection of Claims 66-78 and 81 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 66-78 and 81 have been rejected at pages 21-26 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang, Lim and Andersson. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim, and Andersson disclose the claimed invention as set forth above, including the specifically recited temperature utilized in the process. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang, Lim and Andersson does not support a *prima facie* case of obviousness. Applicants submit that none of the cited references demonstrate that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim and Andersson, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

XIII. The Rejection of Claim 79 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 79 has been rejected at pages 26-27 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang, Lim, Andersson and further in view of Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose a surfactant selected from the recited group. The Office Action attempts to cure these deficiencies with the disclosure of Lemoine, suggesting that Lemoine discloses the use of a polyoxyethylene sorbitan trioleate as a surfactant in the production of alginate microspheres. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang, Lim and Andersson does not support a *prima facie* case of obviousness. Lemoine fails to cure these deficiencies as it provides no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

XIV. The Rejection of Claim 80 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 80 has been rejected at pages 27-29 of the Office Action as allegedly being unpatentable over Zimmermann in view of Huang, Lim and Andersson, and further in view of Vasington and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Huang, Lim and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises 0.75% to 1.5% by weight of sodium alginate or that the sodium alginate is low viscosity. The Office Action attempts to cure these deficiencies with the disclosures of Vasington and Lemoine, indicating

that Vasington and Lemoine disclose the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Huang and Lim does not support a *prima facie* case of obviousness. Andersson, Vasington and Lemoine fail to cure these deficiencies as they provide no showing that the ultrasonic nebulizer of Huang could be utilized in the methods of Zimmermann, or that the combination of Zimmermann and Huang could be utilized with the glass capillary of Lim. Thus, Zimmermann, Huang, Lim, Vasington, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

XV. Conclusion

Applicants believe that the claims of the present application are in condition for allowance and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful in resolving any issues.

With the exception of extension of time fees, no fees are believed due for this submission. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application or credit any overpayment, to Deposit Account No. 50-5071. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-5071.

Respectfully submitted,

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